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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,815	12/07/2000	Akira Aomatsu	5836-01-MJA	5030

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EXAMINER	
KWON, BRIAN YONG S	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 06/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/674,815	AOMATSU, AKIRA	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-28 and 31-39* is/are pending in the application.

4a) Of the above claim(s) *32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-28,31 and 33-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. By Amendment filed May 03, 2006, claims 25 and 34 have been amended and claim 39 has been newly added. Claims 25-28, 31 and 33-39 are currently pending for prosecution on the merits.

Response to Arguments

2. Applicant's arguments with respect to claims 25-28, 31 and 33-38 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 25-28, 31 and 33-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the neutral α amino acid (i.e., glycine, phenylglycine, L-valine, etc...), does not reasonably provide enablement for "an α amino acid". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of

the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The claimed invention is directed to a pharmaceutical composition comprising alpha-amino acid and a 4-amino-3-substitued-butanoic acid such as gabapentin and pregabalin.

It is generally recognized in the art that there exists a physicochemical difference among amino acids. Size, charge and hydropathy of amino acids are known to influence the physicochemical properties of amino acids ("Theoretical Biology and Medical Modelling", BioMed Central, 3:15, 22 March 2006).

Glycine, serine, threonine, cysteine, arginine, lysine and histidine are known as polar neutral amino acid, wherein alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan and methionine are nonpolar (hydrophobic) amino acid; arginine, lysine and histidine are as the positively charged (basic) amino acid; and aspartic acid and glutamic acid are the negatively charged (acidic) amino acid.

The relative skill of those in the art of pharmaceuticals and the unpredictability of the pharmaceutical art is very high. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970). Thus, one having ordinary skill in the art would not have predicted that all of

alpha amino acids would behave similarly to each other without undue amount of experimentation.

The breadth of the claims encompasses numerous possible compounds as being described as alpha amino acid, for example lysine, phenylglycine, hydroxyphenylglycine, dihydroxyphenylglycine, L-alanine, hydroxy-L-alanine, L-leucine, hydroxy-L-leucine, dihydroxy-L-leucine, L-norleucine, methylene-L-norleucine, L-ketonorleucine, L-isoleucine, hydroxy-L-isoleucine, dihydroxy-L-isoleucine, L-valine, hydroxy-L-valine, L-isovaline, L-norvaline, hydroxy-L-norvaline, hydroxy-L-ketonorvaline, L-methionine, L-homomethionine,L-ethionine, L-threonine, acetyl-L-threonine, L-tryptophan, hydroxy-L-tryptophan, methyl-L-tryptophan, L-tyrosine, hydroxy-L-tyrosine, methyl-l—tyrosine. bromo-L-tyrosine, dibromo-L-tyrosine, 3S-diiodo-L-tyrosine, acetyl-L-tyrosine. chloro-L-tyrosine, L-m-tyrosine, L-levodopa, L-methyldopa, L-thyroxine. L-serine, acetyl-L-serine, L-homoserine, acetyl-L-homoserine, ethyl-L-homoserine, propylœ-homoserine, butyl-L-homoserine, L-cydtine, L-homocystine, methyl-L-cystein, allyl-tmcysteine, propyl-L-cysteine, L-phenylalanine, dihydro-L-phenylalanine, hydroxymethyl-L-phenylalanine, L-aminobutyric acid, L-aminoisobutyric acid, L-ketoaminobutyric acid, dichloro-L-aminobutyric acid, dihydroxy-L-aminobutyric acid, phenyl-L-aminobutyric acid, L-aminovaleric acid, L-aminohydroxyvaleric acid, dihydroxy-L-aminovaleric acid, L-aminoisovaleric acid, L-aminohexanoic acid, methyl-L-aminohexanoic acid, L-aminoheptanoic acid, L-aminooctanoic acid, citrulline, L-aspartic acid, L-glutamic acid, L-carbocysteine, L-aminoglutaric acid, L-aminosuccinic acid, L-aminoadipic acid, L-aminopimelic acid, hydroxy-L-aminopimelic acid, methyl-la-aspartic acid, hydroxy-L-aspartic acid, methyl-L-glutamic acid, methylhydroxy-L-glutamic acid. L-methylenegluiamic acid,

hydroxy-la-glutamic acid, dihydroxy-L-glutamic acid, hydroxy-L-aminoadipic acid, L-arginine, L-lysine, L-ornithine, L-canavanine, L-canaline. hydroxy-L-lysine, L-homoarginine, hydroxy-L-ornithine, L-diaminopropionic acid, L-diaminohexanoic acid, L-diaminobutyric acid, L-diaminovaleric acid, L-diaminoheptanoic acid, L-diaminooctanoic acid and etc…

The instant specification discloses that the lactam formation through the intramolecular condensation can be prevented by blocking both the amino acid group and carboxyl group of a 4-amino-3-substutued-butanoic acid derivative such as gabapentin by adding free amino acid as stabilizer in said composition. The specification discloses the use of the specific alpha amino acids, for example glycine and L-valine, in reducing lactam formation in said composition (Examples).

Although the specification provides sufficient number of examples, the specification provides no guidance, in the way of enablement for the full scope of all compounds that are potentially suitable for the invention work similarly as to the tested amino acid. The skill artisan would have not known that which amino acid are capable of accomplishing the desired result of the claimed invention **without undue amount of experimentation**.

As discussed above, the insufficient amount of guidance present in the specification, the nature of the invention, the state of art, the breadth of the claim and the relative skills of the artisan and the predictability of the pharmaceutical art where many specific differences or different physicochemical properties are existed among different class of amino acids would take "undue painstaking experimentation" to practice the invention commensurate in scope with these claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 25-28, 31, 33 and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims in this application introduce a new limitation into the claimed invention, namely "less than 0.5% by weight". The examiner determines that when all evidences in the original disclosure are considered and carefully reviewed, the newly amended claims fail to find support in the original specification.

The specification discloses various lactam contents expressed in term of % by weight based on gabapentin over lapse of time in response to the addition of the amino acid (e.g., glycine and L-valine). For example, Tables 3 and 4 show (I) 0.528 (untreated), 0.220 (treated with glycine) and 0.227 (treating L-valine) and (ii) 0.543 (untreated) and 0.375 (treated with glycine and xylitol) at 45°C/2 weeks (sealed), respectively.

Accordingly to the Tables 3 and 4, the corresponding lactam contents compared to the initial amount of the gabapentin are 0.308% (0.528 – 0.220), 0.301% (0.528 – 0.227) and 0.171% (0.543-0.375), respectively.

As discussed above, there is no express statement about the limitation of "less than 0.5% by weight" that can be found in the specification. The limitation recited in the present claims,

which did not appear in the specification filed, introduces new concepts and violate the description requirement of the first paragraph of 35 USC 112.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 25-27, 29 and 31 are rejected under 35 USC 102(b) as being anticipated by Woodruff (US 5084479).

Woodruff discloses a solution comprising N-methyl-D-aspartic acid and gabapentin with presence of TTX (column 8, lines 4-14).

Since the interpretation of the instant claims allows for the inclusion of any other unspecified ingredients even in major amounts in said composition, the referenced final solution containing N-methyl-D-aspratic acid, gabapentin and water, with the presence of TTX, anticipates the claimed invention.

Since the interpretation of the instantly required "less than 0.5% by weight" allows for the inclusion of zero amount of lactam present in said composition, the referenced composition anticipates the claimed invention.

6. Claims 34, 38 and 39 are rejected under 35 USC 102(a) as being anticipated by Augart et al. (US 6054482).

Augart discloses a pharmaceutical composition consisting essentially of gabapentin in the free amino acid and adjuvants, wherein the amount of corresponding lactam is less than 0.5% by weight in said composition (claims 7-8). Augart also teaches the preparation of said pharmaceutical composition in solid dosage forms including tablet and capsule (claims 9-10).

Since amino acids are alpha (position of the amine) and L (stereochemistry) amino acid in nature, the referenced composition anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable Augart et al. (US 6054482) in view of Robson et al. (US 4126684), and further in view of Costa et al. (US 5248678) and Bays et al. (WO 96/11680).

Augart discloses a pharmaceutical composition consisting essentially of gabapentin in free amino acid and adjuvants, wherein the amount of corresponding lactam is less than 0.5% by weight in said composition (claims 7-8). Augart also teaches the preparation of said pharmaceutical composition in solid dosage forms including tablet and capsule (claims 9-10).

Robson discloses a composition comprising 4-amino-3-substituted butanoic acid derivative such as baclofen, alpha amino acid such as glycine, auxiliary agent (i.e., sorbitol, mannitol, lactose, etc...) and aqueous gelatin solution, wherein said composition is prepared in various dosage forms including tablet, capsule and solution (column 3, line 54 thru column 4, line 11 and Example 2).

Costa is being supplied as the reference to demonstrate the art recognized functional equivalent of gabapentin and baclofen as GABA agonists.

The teaching of Augart differs from the claimed invention (i) in the inclusion of alpha amino acid such as glycine in a composition and (ii) the specific amount of alpha-amino acid (e.g., glycine) in said composition. To incorporate such teaching into the teaching of Augart, would have been obvious in view of Robson who teaches the use of glycine in 4-amino-3-substituted butanoic acid derivative (i.e., baclofen) and Costa who teaches the use of gabapentin as functional equivalent of baclofen as a GABA agonist.

It would have been obvious to a person of ordinary skill in the art at the time of the invention was made to include alpha amino acid such as glycine as taught by Robson et al. in composition of Augart. One of ordinary skill in the art would have expected that the incorporation of glycine as alpha amino acid would not change the physicochemical property of Augart composition. Furthermore, since the equivalence of gabapentin and baclofen as GABA

agonist is well known in the art, the selection of any of known GABA agonists from limited examples of Costa to arrive at the claimed invention would be within the level of ordinary skill in the art.

In addition, optimization of amounts of known active and/or inactive ingredients in a composition or determination of the specific delivery dosage form having optimum therapeutic index is well considered within the skill of the artisan, absent evidence to the contrary.

Although the instant claims use the different names for the said ingredients than those taught in the cited references, these references are particularly pertinent and relevant because all the claimed species and their roles are well taught in the cited reference. Thus, one would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

8. Claims 25-28, 31 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Augart et al. (US 6054482) in view of Robson et al. (US 4126684), and further in view of Costa et al. (US 5248678) and Bays et al. (WO 96/11680).

The modified teaching of Augart includes all that is recited in claims 25-28, 31 and 33 except the preparation of said composition in liquid formulation.

Bays is being supplied as the reference to demonstrate the routine knowledge in preparing 4-amino-3-substitued butanoic acid derivative (i.e., gabapentin) in various dosage forms including solid or liquid dosage form (page 1, lines 24-34; page 3, line 24 thru page 5, line 17).

However, those of ordinary skill in the art would have been readily optimized effective dosages forms including liquid dosage forms as determined by good medical practice and the clinical condition of the individual patient. One having ordinary skilled in the art would have been motivated to make such modification to extend the usage of said composition in liquid dosage forms to accommodate patient's preference and needs where the compliance could be improved with effective and well tolerated drug.

One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 25-28, 31 and 33-39 are rejected provisionally under the judicially created doctrine of double patenting over claims 36-37 of Copending US Application No. 09/674,819.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the claimed composition is overlapping with the claimed scope of the copending application. Since the interpretation of the instant claim allows for the inclusion of any other unspecified ingredients even in major amounts in said composition, the presence of humectant and auxiliary agent (e.g., neutral amino acid, see page 49, lines 13-15 of the specification) in said composition in the copending application makes obvious the instant claims.

With respect to the determination of concurrent dosage forms, particularly liquid form, those of ordinary skill in the art would have been readily optimized effective dosages forms including liquid dosage forms as determined by good medical practice and the clinical condition of the individual patient. One having ordinary skilled in the art would have been motivated to make such modification to extend the usage of said composition in liquid dosage forms to accommodate patient's preference and needs where the compliance could be improved with effective and well tolerated drug.

Since the interpretation of the instantly required "less than 0.5% by weight" allows for the inclusion of zero amount of lactam present in said composition, the copending application makes obvious the instant invention.

Conclusion

10. No Claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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